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PATENT DEPARTMENT, MS8260-1611
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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

NOTIFICATION DATE	DELIVERY MODE
03/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

~IPGSGro@pfizer.com

Office Action Summary	Application No.	Applicant(s)	
	10/542,184	DAVIES ET AL.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-32* is/are rejected.

7)☒ Claim(s) *1,5,6,13,20,22,25,27,29,30 and 32* is/are objected to.

8)☒ Claim(s) *1-32* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: PTO-90C Sequence Compliance Letter; PTO-Notice to Comply with the Sequence Disclsoure Requirements.

DETAILED ACTION

Status of Application, Amendments and/or Claims

As noted in the decision mailed on 8/7/08, the petition under 37 C.F.R. § 1.137(b) to revive the instant application has been granted. The response filed on 7/21/08 (election in response to restriction requirement) has been entered.

Claims 1-32 are pending in the instant application.

Election of species

Two elections of species were required in the Office Action mailed 7/27/07.

(I) The first election required elections of two NGF responsive genes, and indication of whether each was "enhanced" or "diminished" as recited in claims 9 and 11. Applicants' election with traverse of the species of (a) substance P (up-regulated) and (b) galanin (down-regulated) in the reply filed on 7/21/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the requirement for election of species, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants generally state that "claims 1-32 read on the elected species". With respect to the first species election, the Examiner agrees except with respect to claim 12, which does not include galanin as one of the recited genes that are diminished.

Claim 12 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

(II) The second election required election of a species of neuron, and indication of whether the species was a nociceptive neuron as encompassed by claims 21 and 28. Applicants' election with traverse of the species of Dorsal Root Ganglia (nociceptive) in the reply filed on 7/21/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the requirement for election of species, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicants generally state that "claims 1-32 read on the elected species". With respect to the second species election, the Examiner agrees with this statement.

Claims 1-11 and 13-32 are under consideration, as they read upon the elected species.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). This application fails to comply with the requirements of 37 CFR 1.821 through 1.825.

Specifically, the specification discloses nucleic acid sequences (primers) at page 19 (5 sequences); page 20 (3 sequences) and page 26 (8 sequences) that have not been submitted as part of a "Sequence Listing" as required by the sequence rules (37 CFR 1.821 - 1.825). The Examiner notes that no Sequence Listing has yet been filed in the instant application.

Therefore, Applicants must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) by submitting an initial computer-readable form (CRF) of a "Sequence Listing" containing each sequence disclosed in the specification and/or drawings; a paper copy of the "Sequence Listing", as well as an amendment specifically directing its entry into the application; and a statement that the content of the paper and CRF copies are the same, and include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

Furthermore, the specification must be amended such that each sequence shown therein is accompanied by the appropriate corresponding sequence identifier.

Please see attached PTO-90C and Revised Notice to Comply.

Specification

The disclosure is objected to because of the following informalities:

As described above, each sequences disclosed in the specification (pages 19, 20 and 26) must each include a corresponding sequence identifier representing a sequence present in the sequence listing.

Appropriate correction is required.

Claim Objections

Claims 1, 5, 6, 13, 20, 22, 25, 27, 29, 30 and 32 are objected to because of the following informalities:

(1) Claims 1 and 20 should clearly indicate that the name "Nerve Growth Factor" and the acronym "NGF" are the same by amending line 4 to recite "...Nerve Growth Factor (NGF)...".

(2) Claim 6 recites, "...the neurons in the culture are between about between about 3.5 cells per square millimeter to about 35 cells per square millimeter or 3.5 cells per square millimeter to about 35 cells per square millimeter." This recitation is objected to because the claim limitations are unnecessarily redundant: (a) "between about" is repeated twice in a row (lines 1-2) and "3.5 cells per square millimeter to about 35 cells per square millimeter" is also repeated twice in a row (lines 2-3).

(3) In claims 5 and 30, the usage of "about 100- to about..." is objected to because the dash after each 100 is unnecessary. For example, claim 23 recites "...between about 100 to about 200" without using any dashes after the 100.

(4) Claims 13 and 25 are objected to because the term "substance P" is improperly capitalized (twice in each claim) as "Substance P". Claim 10 correctly uses "substance P". The relevant art uses "substance P" (see pg 181 of Winston et al (2001. Pain 89: 181-186).

(5) Claims 22 and 29 are objected to because "dorsal root ganglion" is not capitalized in a manner similar to the usage of "Dorsal Root Ganglia" in claims 3 and 4.

(6) Independent claim 27 should clearly indicate the full name of the acronym NGF by amending line 4 to recite "...NGF (Nerve Growth Factor)...".

(7) Claim 32 is objected to for using the abbreviation "sppr 1" instead of "sppr1A" (Claims 13 and 25 both use "small proline rich repeat protein 1A (sppr1A)").

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 13-19 and 27-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because it does not include a method step that clearly achieves the goal set forth in the preamble of the claim ("assessing the ability of a candidate agent to modulate NGF activity"). The last two lines of the claim recite "wherein an alteration of the level of expression of the two or more genes indicates the therapeutic potential of the candidate agent", which is a different goal then set forth in the preamble of the claim. Compare this with the preamble and concluding statements of claim 20, where the concluding statement clearly relates to the goal set forth in the preamble.

Claim 10 recites the limitation "the gene" in line 1. The antecedent basis of this recitation is unclear. Specifically, it is unclear which gene recited in the parent claims is being referred to. Parent claim 1 recites "two or more NGF responsive genes". Claim 9, which depends from claim 1 and is the parent of claim 10, recites "wherein expression of at least one gene of the two or more genes is enhanced". It is unclear whether "the gene" of claim 10 is the enhanced gene of claim 9, or one of the other genes encompassed by claims 1 and 9.

Claim 27 is rejected for the same reason as claim 1 above.

The remaining claims are rejected for depending from an indefinite claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 7-9, 11, 15, 27-29 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Winston et al, 2001. Pain 89: 181-186).

The recitation of "indicates the therapeutic potential of the candidate agent" in the concluding sentence of claims 1 and 27 from the instant application is interpreted as an intended use and bears no accorded patentable weight to distinguish the claimed method over one from the prior art.

Winston et al teach cultures of primary neuronal culture of nociceptive neurons of Dorsal Root Ganglia that express the high-affinity trkA receptor (in particular, see Abstract on pg 181 and Materials and Methods on pg 182). Winston et al further teach a method comprising contacting said cultures with Nerve Growth Factor (NGF) and a candidate agent (specifically, the trkA inhibitor k252a) and measuring the level of two NGF responsive genes in said culture (specifically, the genes VR-1 and CGRP; see section 3.3 and Figure 3 on pg 184). The expression of each gene increases in the presence of Nerve Growth Factor, and this expression is diminished in the presence of Nerve Growth Factor plus k252a. As such, Winston et al teach a method that meets all of the limitations of claims 1-4, 9, 11 and 27-29.

Winston et al use 10,000-20,000 neurons/well in the neuronal cultures (pg 182, first column). Claim 5 recites, "neurons in the culture are between about 100- to about 1000 cells per wells". The instant specification does not provide a limiting definition of the term "about 1000"; therefore, this term is broadly interpreted as encompassing 10,000. As such, Winston et al also teach a method that meets all of the limitations of claim 5.

Winston et al use NGF concentrations of 10, 30, 100 and 300 ng/ml (see Figure 3). Therefore, Winston et al also teach a method that meets all of the limitations of claims 7, 8 and 31.

Winston et al further teach isolating RNA from the neurons and detecting the RNA on a Northern Blot (see Figure 4B). Therefore, Winston et al also teach a method that meets all of the limitations of claim 15.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5, 6 and 30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) as (for claims 5 and 6) applied to claim 1 above, or (for claim 30) as applied to claim 27 above, and further in view of Kerekes et al (2000. Journal of Autonomic Nervous System. 81: 128-138).

Claim 5 depends from claim 1 and in one embodiment limits the method to one wherein the cultured neurons are between about 100 to about 200 cells per well. [It is noted that claim 5 is also rejected under 35 U.S.C. 102(b) as anticipated by Winston et al (2001) based on the embodiment "about 100- to about 1000 cells per well"]. Claim 6 depends from claim 5 and limits the method to one wherein the cultured neurons are between about 3.5 cells per square millimeter to about 35 cells per square millimeter. Claim 30 depends from claim 27 and limits the method of the parent claim to one wherein "the neurons in the culture are about 100- to about 200 cells per well or 3.5 cells per square millimeter to about 7 cells per square millimeter".

The teachings of Winston et al (2001) are described above, including the teachings that anticipate instant claims 1 and 27. Winston et al do not teach the further limitations that the cultured neurons are about 100- to about 200 cells per well (claims 5 and 27), or between about 3.5 cells per square millimeter or to about 35 cells per square millimeter (claim 6) or between about 3.5 cells per square millimeter or to about 7 cells per square millimeter (claim 27).

Kerekes et al further teach that "[t]he aim of the present study was to analyse to what extent NPY expression, just as that of VIP ... and galanin ... is increased when DRG neurones are put in culture" (pg 129). Kerekes et al teach the "effect of neurotrophic factors on neuropeptides Y (NPY) expression" in "adult rat dispersed dorsal root ganglion cultures" (see Abstract); the factors include nerve growth factor

(NGF). Furthermore, Kerekes et al teach that "NPY expression was also influenced by cell density" and "[t]he results showed an effect of cell density on NPY expression, whereby fewer neurones expressed NPY in high than in low density culture. This difference was seen in untreated as well as growth factor-treated cultures" (see Abstract). Kerekes et al further teach that low-density cultures have 10-300 neurones/chamber (pg 131). The instant specification does not provide a limiting definition of the term "well"; therefore, it is interpreted broadly to encompass a "chamber" for culturing neurons. Kerekes et al further teach that each chamber of the eight-chambered slides has a 0.7 cm^2 culturing area (pg 129), which is equivalent to 70 mm^2 (square millimeter). Thus, the low density cultures taught by Kerekes et al have 10 to 300 cells per 70 square millimeter, or 0.14 to 4.28 cells per square millimeter. These cell numbers and densities are encompassed by each of the ranges recited in each of claims 5, 6, and 30.

It would have been obvious at the time the invention was made to practice the method of claim 1 or 27 taught by Winston et al, but with a low-density cell culture as taught by Kerekes et al substituting for the cell culture taught by Winston et al. The person having ordinary skill in the art would have been motivated to make this modification because Kerekes et al teach that low density cultures can result in increased expression of products expressed by cultured cells of the same type taught in Winston et al (dorsal root ganglion neurons). Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success because such a change requires simple substitution of the cell density taught by Kerekes et al for the cell density in the culture in the screening method taught by Winston et al.

Claims 10 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) as (for claim 10) applied to claim 9 above, or (for claim 32) as applied to claim 27 above.

Claim 10 depends from claim 9 and encompasses a method wherein one of the two or more genes is "substance P", which is one of the two elected species of genes. Applicants indicate that expression of substance P is enhanced in the presence of NGF.

Claim 32 depends from claim 27 and similarly encompasses a method wherein one or more gene is "substance P".

The teachings of Winston et al (2001) are described above, including the teachings that anticipate instant claims 9 and 27. Winston et al further teach that "NGF regulation of VR-1 mRNA together with previous reports of NGF regulation of mRNA for the neuropeptides substance P and CGRP and the tetrodotoxin resistant sodium channel SNS/PN3 ... supports a model in which NGF increases the sensitivity of nociceptors in part by increasing mRNA levels of nociceptive genes" (pg 186). As described above, Winston et al teach a method of claim 9 or 27 wherein the genes are VR-1 and CGRP, but Winston et al do not specifically teach a method of claim 9 or 27 wherein one of the genes is substance P.

It would have been obvious at the time the invention was made to include an additional measurement of substance P in addition to the measurements of VR-1 and CGRP in the method of claim 9 or 27 taught by Winston et al. The person having ordinary skill in the art would have been motivated to make this modification because Winston et al teach that substance P is similarly regulated by NGF as VR-1 and CGRP, and thus the skilled artisan would be motivated to determine if this NGF-responsive gene also has its expression modulated by the trkA inhibitor k252a. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success because Winston et al teach that measurement of substance P expression is known in the art and measuring substance P would require simply measuring the expression of one additional gene.

Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) as applied to claim 1 above, and further in view of Corness et al (1998. NeuroReport. 9: 1533-1536).

Claim 13 depends from claim 1 and encompasses a method wherein the two or more genes comprise substance P and galanin, which are the two elected species of genes. Applicants indicate that expression of substance P is enhanced in the presence of NGF, and expression of galanin is diminished.

The teachings of Winston et al are described above. Winston et al further teach that "NGF regulation of VR-1 mRNA together with previous reports of NGF regulation of mRNA for the neuropeptides substance P and CGRP and the tetrodotoxin resistant sodium channel SNS/PN3 ... supports a model in which NGF increases the sensitivity of nociceptors in part by increasing mRNA levels of nociceptive genes" (pg 186). As described above, Winston et al teach a method of claim 1 wherein the genes are VR-1 and CGRP, but Winston et al do not specifically teach a method of claim 1 wherein one of the genes is substance P and one of the genes is galanin.

Corness et al teach "in culture, incubation of adult DRG neurons in the presence of NGF results in a decreased number of galanin and galanin mRNA-positive neurons in adult DRG culture" (pg 1535). Corness et al further teach "synthesis of peptides such as substance P and CGRP strongly depend on the continuous supply of NGF" (pg 1535).

It would have been obvious at the time the invention was made to include measurement of galanin (as taught by Corness et al) and substance P (as taught by both Winston et al and Corness et al) in addition to the measurement of VR-1 and CGRP in the method of claim 1 taught by Winston et al. The person having ordinary skill in the art would have been motivated to make this modification because both Winston et al and Corness et al teach that substance P is similarly regulated by NGF as VR-1 and CGRP, and Corness et al teach that galanin is inversely regulated by NGF, and thus the skilled artisan would be motivated to determine if these NGF-responsive genes also have their expression modulated by the trkA inhibitor k252a. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success because Winston et al and Corness et al teach that measurement of substance P and galanin expression is known in the art and measuring substance P and galanin in addition to VR-1 or CGRP would require simply measuring the expression of two genes in addition to the others.

Claims 14, 20-22, 24 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) as applied to claim 1 above, and further in view of Debeir et al (1999. Proc Natl Acad Sci USA. 96: 4067-4072).

Claim 14 depends from claim 1 and limits the candidate compound to an antibody. Claim 20 is an independent claim but is directed to a method that is a narrower embodiment of claim 1; specifically, it recites all of the limitations of claim 1 with the additional limitation that "two or more candidate agents are used". Claims 21, 22, 24 and 26 depend from claim 20 and recite limitations analogous to claims that depend from claim 1 (claims 3, 4, 8 and 14).

The teachings of Winston et al are summarized above. Winston et al do not teach a method using candidate compound that is an antibody, or a method using a combination of two candidate compounds.

Debeir et al teach an anti-NGF monoclonal antibody that is TrkA antagonist (see Abstract).

With respect to claim 14, it would have been obvious at the time the invention was made to practice the method taught by Winston et al but to replace the trkA inhibitor k252a with the anti-NGF antibody taught by Debeir et al. The person having ordinary skill in the art would be motivated to make this modification to determine whether the results observed with k252a could be observed with other known antagonists of the NGF-TrkA interaction. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success because such a change requires a simple substitution of one compound with a known functional activity (antagonism) for another.

With respect to claims 20-22, 24 and 26, it would have been obvious at the time the invention was made to practice the method taught by Winston et al but to use the anti-NGF antibody taught by Debeir et al in combination with the trkA inhibitor k252a. The person having ordinary skill in the art would be motivated to make this modification because k252a does not completely antagonize the response of the cells to NGF (as shown in Figure 4 of Winston et al) and therefore including the second antagonist would determine whether the activity of the trkA receptor in response to NGF could be further inhibited by addition of the second antagonist compound (anti-NGF antibody). Furthermore, a person of ordinary skill in the art would have had a reasonable expectation of success because such a change requires a simple addition of one

compound with a known functional activity (antagonism) to a method of using another such compound.

Claims 16 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) as applied to claim 15 above, and further in view of U.S. Patent 6,218,531 (Ekenberg et al, published 4/17/01).

Claim 16 depends from claim 15 and limit the method of RNA isolation to one using silica based magnetic beads that bind RNA under high salt conditions and wherein the silica based magnetic beads are washed with about 80% ethanol. Claim 17 depends from claim 16 and limits the method to one wherein the isolated RNA is detected by PCR using intron-spanning primers.

The teachings of Winston et al are summarized above. Winston et al do not teach use of magnetic beads for RNA isolation.

Ekenberg et al teach use of a silica matrix for RNA isolation, wherein said silica matrix is in the form of magnetic beads coated with silica (column 5, lines 38-41). Ekenberg et al further teach use of a "sufficiently high concentration of a chaotropic salt to promote the binding of RNA with the silica matrix" (column 6, lines 8-10). Ekenberg et al further teach use of an ethanol wash of "most preferably at least 50% by volume", which is encompassed by the phrase "about 80%" recited in claim 16. Ekenberg et al further teach an example of RNA detection by PCR using "a primer pair which hybridizes to an encoding region" and "which flanks at least one intron" (see Example 6). Ekenberg et al further teach that the "RNA isolation method of the present invention produces a high yield of RNA, and is less labor intensive than conventional RNA isolation techniques" (column 7, lines 13-15).

It would have been obvious at the time the invention was made to substitute the RNA isolation and detection method taught by Ekenberg et al for RNA isolation and detection in the method taught by Winston et al. The person having ordinary skill in the art would have been motivated to make this modification because the bead isolation method is less labor intensive than conventional RNA isolation techniques, such as those used by Winston et al. Furthermore, a person of ordinary skill in the art would

have had a reasonable expectation of success because the change requires a simple substitution of one known technique of RNA isolation and detection for another.

Claims 18 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) as applied to claim 1 above, and further in view of Dickens et al (1997. Journal of Neuroscience Research. 47: 271-276).

Claim 18 depends from claim 1 and limits the candidate agent to one dissolved in an organic solvent. Claim 19 depends from claim 18 and limits the organic solvent to dimethyl sulphoxide (DMSO).

The teachings of Winston et al are summarized above. Winston et al are silent as to the organic solvent in which k252a is dissolved.

Dickens et al teach administration of k252a dissolved in DMSO to PC12 neuronal cells (Figure 4 on page 274).

It would have been obvious at the time the invention was made to practice the method taught by Winston et al using k252a dissolved in DMSO. The person having ordinary skill in the art would be motivated to make this modification because Winston et al do not teach what solvent that k252a should be dissolved, and Dickens et al teach that the proper solvent is the organic solvent DMSO. Further, a person of ordinary skill in the art would have had a reasonable expectation of success because such a change merely adds necessary information to the method that Winston et al is silent in regard to, and dissolving a compound in the appropriate solvent is standard in the art.

Claim 23 is rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) in view of Debeir et al (1999. Proc Natl Acad Sci USA. 96: 4067-4072) as applied to claim 20 above, and further in view of Kerekes et al (2000. Journal of Autonomic Nervous System. 81: 128-138).

As described above, claim 20 is an independent claim but is directed to a method that is a narrower embodiment of claim 1; specifically, it recites all of the limitations of claim 1 with the additional limitation that "two or more candidate agents are used". Claim 23 depends from claim 20 and limits the method of the parent claim to one

wherein "the neurons in the culture are about 100- to about 200 cells per well or 3.5 cells per square millimeter to about 7 cells per square millimeter".

The teachings of Winston et al (2001) are described above, including the teachings that anticipate instant claim 1. Winston et al do not teach a combination of two candidate compounds. Winston et al do not teach the further limitation that the neurons in the culture are about 100- to about 200 cells per well.

Debeir et al teach an anti-NGF monoclonal antibody that is TrkA antagonist (see Abstract).

Kerekes et al further teach that "[t]he aim of the present study was to analyse to what extent NPY expression, just as that of VIP ... and galanin ... is increased when DRG neurones are put in culture" (pg 129). Kerekes et al teach the "effect of neurotrophic factors on neuropeptides Y (NPY) expression" in "adult rat dispersed dorsal root ganglion cultures"; the factors include nerve growth factor (NGF). Furthermore, Kerekes et al teach that "NPY expression was also influenced by cell density" and "[t]he results showed an effect of cell density on NPY expression, whereby fewer neurones expressed NPY in high than in low density culture. This difference was seen in untreated as well as growth factor-treated cultures" (see Abstract). Kerekes et al further teach that low-density cultures have 10-300 neurones/chamber (pg 131). The instant specification does not provide a limiting definition of the term "well"; therefore, it is interpreted broadly to encompass a "chamber" for culturing neurons. Kerekes et al further teach that each chamber of the eight-chambered slides has a 0.7 cm^2 culturing area (pg 129), which is equivalent to 70 mm^2 (square millimeter). Thus, the low density cultures taught by Kerekes et al have 10 to 300 cells per 70 square millimeter, or 0.14 to 4.28 cells per square millimeter. These cell numbers and densities are encompassed by the ranges recited in claim 23.

It would have been obvious at the time the invention was made to practice the method of claim 1 taught by Winston et al but to use the anti-NGF antibody taught by Debeir et al in combination with the trkA inhibitor k252a, and to further use a low-density cell culture as taught by Kerekes et al. The person having ordinary skill in the art would have been motivated to make this modification because (1) k252a does not completely

antagonize the response of the cells to NGF (as shown in Figure 4 of Winston et al) and therefore including the second antagonist would determine whether the activity of the trkA receptor in response to NGF could be further inhibited by addition of the second antagonist compound (anti-NGF antibody) and (2) the low density cultures taught can result in increased expression of products expressed by cultured dorsal root ganglion neurons. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success because such changes require only (1) simple addition of one compound with a known functional activity (antagonism) to a method of using another such compound and (2) simple substitution of the cell density taught by Kerekes et al for the cell density in the culture in the screening method taught by Winston et al.

Claim 25 is rejected under 35 U.S.C. 103(a) as being unpatentable over Winston et al (2001. Pain 89: 181-186) in view of Debeir et al (1999. Proc Natl Acad Sci USA. 96: 4067-4072) as applied to claim 20 above, and further in view of Corness et al (1998. NeuroReport. 9: 1533-1536).

As described above, claim 20 is an independent claim but is directed to a method that is a narrower embodiment of claim 1; specifically, it recites all of the limitations of claim 1 with the additional limitation that "two or more candidate agents are used". Claim 25 depends from claim 20 and limits the method of the parent claim to one wherein the two or more genes comprise substance P and galanin, which are the two elected species of genes. Applicants indicate that expression of substance P is enhanced in the presence of NGF, and expression of galanin is diminished.

The teachings of Winston et al (2001) are described above, including the teachings that anticipate instant claim 1. Winston et al further teach that "NGF regulation of VR-1 mRNA together with previous reports of NGF regulation of mRNA for the neuropeptides substance P and CGRP and the tetrodotoxin resistant sodium channel SNS/PN3 ... supports a model in which NGF increases the sensitivity of nociceptors in part by increasing mRNA levels of nociceptive genes" (pg 186). As described above, Winston et al teach a method of claim 1 wherein the genes are VR-1 and CGRP, but Winston et al do not specifically teach a method of claim 1 wherein one

of the genes is substance P and one of the genes is galanin. Winston et al do not teach a combination of two candidate compounds.

Debeir et al teach an anti-NGF monoclonal antibody that is TrkA antagonist (see Abstract).

Corness et al teach "in culture, incubation of adult DRG neurons in the presence of NGF results in a decreased number of galanin and galanin mRNA-positive neurons in adult DRG culture" (pg 1535). Corness et al further teach "synthesis of peptides such as substance P and CGRP strongly depend on the continuous supply of NGF" (pg 1535).

It would have been obvious at the time the invention was made to practice the method of claim 1 taught by Winston et al but to use the anti-NGF antibody taught by Debeir in combination with the trkA inhibitor k252a, and to further include measurement of galanin (as taught by Corness et al) and substance P (as taught by both Winston et al and Corness et al) in addition to the measurement of VR-1 and CGRP in the method of claim 1 taught by Winston et al. The person having ordinary skill in the art would have been motivated to make this modification because (1) k252a does not completely antagonize the response of the cells to NGF (as shown in Figure 4 of Winston et al) and therefore including the second antagonist would determine whether the activity of the trkA receptor in response to NGF could be further inhibited by addition of the second antagonist compound (anti-NGF antibody) and (2) both Winston et al and Corness et al teach that substance P is similarly regulated by NGF as VR-1 and CGRP, and Corness et al teach that galanin is inversely regulated by NGF, and thus the skilled artisan would be motivated to determine if these NGF-responsive genes also have their expression modulated by the trkA inhibitor k252a and the anti-NGF antibody. Furthermore, a person of ordinary skill in the art would have a reasonable expectation of success because such changes require only (1) simple addition of one compound with a known functional activity (antagonism) to a method of using another such compound and (2) require simply measuring the expression of two genes (substance P and galanin) in addition to the others (VR-1 or CGRP), and because Winston et al and Corness et al teach that measurement of substance P and galanin expression is known in the art.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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